



Attorney's Docket No. 048777/277097

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: CONTRAST MEDIA FOR USE IN MEDICAL AND DIAGNOSTIC PROCEDURES
AND METHODS OF USING THE SAME. .

Appl No.:	10/679,052	Confirmation No.:	7084
Filed:	October 2, 2003	Group Art Unit:	1618
For:	Archie B. Williams, III	Examiner	Leah H. Schlientz

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration Under 37 CFR § 1.132

Introduction

I, Archie B. Williams III, declare that:

1. I am the inventor of U.S. Patent Appl. No. 10/679,052, filed October 3, 2003. Also, I am employed by E-Z-EM, Inc., the assignee of record of the '052 application. I am currently Vice President Clinical Affairs and Medical Community Liaison for E-Z-EM. I have been employed by E-Z-EM in various capacities for twenty-eight (28) years.

2. I have read the Official Action of June 6, 2007 and the references relied upon by the Examiner.

3. I am submitting this declaration to show certain unexpected results of the claimed invention, which are not suggested in the references relied upon by the Examiner.

4. I am also submitting this declaration to show that the claimed invention satisfies a long felt need for contrast agents having the properties of the claimed invention.

5. A true copy of each publication cited herein is attached hereto as an Exhibit and each such exhibit is numerically referenced herein.

The Claimed Invention

6. I have reviewed the claims as currently amended. The scope of these claims cover a commercially available contrast agent known as VoLumen®. E-Z-EM manufactures and sells VoLumen® in the United States. E-Z-EM began selling this product in the United States in July, 2004.

7. VoLumen® is a 0.1% w/v barium sulfate neutral oral contrast agent. It also consists of about 2.0% w/v sorbitol. Its unexpected improved properties over prior art contrast agents result from combining a low concentration of barium sulfate with a sugar alcohol (e.g. sorbitol). We have observed that such a combination, when administered to a patient, leads to increased distention of an anatomic segment together with enhanced contrast, thus allowing physicians to detect certain abnormalities that could not be detected using oral contrast agents known in the art.

Superiority of the Claimed Invention Over Oral Contrast Agents Known in the Art

8. I understand that each independent claim has been amended to recite a weight percent range of sugar alcohol. The claims have also been amended to require that the claimed invention be in the form of an aqueous suspension. The Nyman reference discloses the use of a 1.7% w/v barium sulfate suspension known as E-Z-CAT®. Another commercially available barium suspension is Read-Cat® which contains a 1.3% w/v barium sulfate concentration. E-

Z-EM, manufactures and markets both E-Z-CAT® and Read-Cat® in the United States. E-Z-CAT® contains additives similar to those in Read-Cat, such as sorbitol. Specifically, the E-Z-CAT® suspension contains about 1.8% w/v sorbitol. Read-Cat® contains about 2.6% w/v sorbitol.

9. The Falash reference (DD23830 (abstract)) discloses a barium sulfate suspension. However, the Falash composition contains no sugar alcohol. Also, Fuisz (U.S. Pat. No. 6,337,082) does not disclose an aqueous suspension comprising a low concentration of barium sulfate in combination with a sugar alcohol. Therefore, to my knowledge and in my opinion, the closest prior art in terms of barium concentration and the amount of sugar alcohol in an aqueous suspension is E-Z-CAT® and Read-Cat®, as compared to the prior art relied upon by the Examiner. The claimed invention possesses unexpected improved imaging and luminal distention properties over these products, as discussed below.

10. Nyman's E-Z-CAT® (1.7% w/v BaSO₄) and Read-Cat® (1.3% w/v BaSO₄) differ in barium concentration by 0.4% w/v. As contrast agents, both products possess similar drawbacks with respect to luminal distention and imaging of the digestive tract, including but not limited to the stomach, large intestine and the bowel wall. For example, both E-Z-CAT® and Read-Cat® exhibit about the same level of brightness on a CT Scan. This is because their respective barium sulfate concentrations exceed at least 1.0% w/v. It has been reported that contrast agents having at least 1.0% w/v barium sulfate can obscure certain regions of the bowel during an imaging procedure. This set back is illustrated by the CT images below.

11. Specifically, these images show the difference between an oral contrast agent having $>1.0\%$ w/v barium sulfate (Readi-Cat®) (Image A) and an agent having $<1.0\%$ w/v barium sulfate (VoLumen®) (Image B), in the same patient. Here, the patient in this study has a diseased segment of the bowel (sigmoid). Specifically, a 54-year-old female with Chrohn's disease and fistula was subject to two separate multi-detector computer tomography ("MDCT") examinations. In each examination, the patient was administered 900 ml to 1,000 ml of either Readi-Cat® or VoLumen® over a 45-minute period. Immediately prior to scanning the patient, an additional 7 ounces (207 ml) was administered to distend the stomach. Figures A and B represent images taken from the two separate examinations.

12. In Figure A, the bright white oral contrast is obscuring the surrounding soft tissue and enhancement of the bowel wall. In the VoLumen® image (Figure B), enhancement of the mucosal surface is observed. This image shows inflammation/active disease in the internal bowel wall lining (mucosa) and edema in the thickened walls, as well as lesions in the lumen, which are obscured by the oral contrast with barium concentrations exceeding 1.0% w/v (Figure A).

Figure A.



Figure B.



13. The above CT images demonstrate the unexpected improved imaging and luminal distention properties of the claimed invention, namely a contrast agent having a sugar alcohol, in combination with a low concentration of barium sulfate ($\leq 0.5\%$ w/v), versus the prior art such as Read-Cat® (1.3% w/v), as well as E-Z-CAT® (1.7% w/v), which is disclosed in Nyman.

14. The attached publication (Ex.1) further demonstrates that the claimed composition possesses an unexpected high degree of luminal distention and imaging, which is not suggested by the cited prior art. This publication is entitled "Evaluation of Bowel Distention and Bowel Wall Appearance by Using Neutral Oral Contrast Agent for Multi-Detector Row CT", *Radiology*: Volume 238: Number 1- January 2006 (hereafter the "Megibow study")¹. In this study, the performance of VoLumen® as a bowel-marker agent is compared to the prior art barium suspension, Read-Cat®. As mentioned, the barium concentration of VoLumen® and Read-Cat® is 0.1% and 1.3%, respectively. Also, VoLumen® contains additives similar to those in Read-Cat®, as mentioned above.

15. The Megibow Study shows that the maximal distension in the stomach, duodenum, jejunum, ileum and small bowel after administration of VoLumen® was significantly higher than that obtained after the administration of Read-Cat®. For example, Table 4 shows the results of a quantitative analysis of patients receiving VoLumen®; Read-Cat®; and

¹ The Megibow study was sponsored by E-Z-EM. The sponsor provided the VoLumen. The sponsor also created all data forms and instructed the physicians and their respective assistants on the randomization process. The sponsor also made random visits to the site to provide quality control monitoring and oversight. The sponsor assumed the costs of the CT scans at the institutional research rate. The authors who were employees of E-Z-EM (Carmela Houston, Micheal Boruch and Archie Williams) were blinded to all data generated during the trial. See Exhibit 1, p.88, Materials and Methods.

water/methylcellulose (Ex. 1, p. 92). These results show that the maximal distention in the duodenum after administration of VoLumen® was significantly higher than that obtained after administration of either Read-Cat® or water/methylcellulose. Also, Figure 1 shows that VoLumen® successfully produced significant visual enhancement within the stomach, duodenum, and small bowel. It also facilitated the detection of disease (*Id.*, p.91.).

16. In sum, the results of the Megibow study show excellent distention and visualization properties of the claimed invention. By combining a low concentration of barium sulfate ($\leq 0.5\%$ w/v) with a sugar alcohol in an aqueous suspension, the difference between the contrast in the bowel and the enhanced soft tissue – bowel wall – is greatly improved. Consequently, the image quality is much improved, such that the true boundary between contrast and soft tissue can be readily discerned. This allows for accurate visualization of the bowel wall, for example, with sufficient contrast enhancement to reveal vascular supply of blood to mucosa, sub mucosa and all layers of the bowel wall, stomach, small bowel and colon, which is not readily achievable with E-Z-CAT®, Read-Cat® or other commercially available contrast agents, to my knowledge.

17. The Megibow study demonstrates that a low concentration of barium sulfate combined with a sugar alcohol in an aqueous suspension possesses an unexpected degree of luminal distention and visualization compared with E-Z-Cat® and Read-Cat®. These unexpected improved results are not suggested in the cited art. Indeed, neither Falasch, Fuisz nor Nyman suggest that significantly reducing the barium concentration, in combination with a sugar

alcohol, would provide an oral contrast agent having such improved properties, as those shown in the Megibow study.

18. Additionally, other commercially available neutral contrast agents (water, PEG and methyl cellulose) have been shown to be inferior to the claimed invention. For example, in comparing VoLumen® with other known contrast agents, it was observed that the distention of the overall GI tract using VoLumen® is significantly better than other neutral contrast agents. Specifically, these studies reported that, when comparing both VoLumen® and water on the same patient populations, VoLumen® significantly improves distention of the stomach, ileum and colon. VoLumen® also improves visualization of bowel wall detail².

19. Other studies have reported that VoLumen® has been shown to provide significantly greater distention when evaluating the gastrointestinal tract when compared to other neutral or positive oral contrast agents, including the stomach, duodenum, jejunum, ileum, and colon³

20. Also, the claimed invention has exhibited much improved diagnostic properties when used with CT enterography. Physicians find it particularly useful to evaluate the small bowel both in routine CT scanning or using a more specific technique called CT Enterography. CT Enterography uses a larger volume of neutral oral contrast agent and intravenous contrast agent. In one study, it was reported that CT Enterography with VoLumen® clearly depicts

² See Exhibit 1 and 2

³ See Exhibits 1, 2, 3, 4, 5 and 6

the small bowel by providing significant distention and visualization for detection of small bowel disease.⁴

The Claimed Invention Satisfies a Long Felt Need

21. The claimed invention satisfies a long felt need for a contrast agent suitable for CT-PET and MRI scanning. To diagnose bowel diseases with imaging techniques, it is essential to distend the bowel and visualize its wall. To my knowledge, prior to the claimed invention, commercially available oral contrast agents were only suitable for CT scanning. To my knowledge, prior to that time, there existed no commercially available oral contrast agents for CT-PET or MRI scanning. CT scanning agents are typically positive contrast agents. It has been reported in the literature that positive contrast agents routinely preclude the visualization of the bowel wall and provide inadequate bowel distention.

22. In patient studies, an oral positive contrast agent (Readi-Cat® 2.1%) and VoLumen® were compared using MRI and CT-PET scanning. In these studies, it was found that VoLumen® produced a significant improvement in distention and wall visualization of the duodenum, jejunum, and ileum.

23. The claimed invention's low concentration of barium in combination with a sugar alcohol makes it suitable for MRI and CT-PET scanning. This is because the claimed invention (e.g. VoLumen®) does not produce artifacts and it enhances the overall diagnosis in both techniques.

24. Also, MR is particularly useful in young patients due to the lack of radiation and better soft tissue contrast especially in cases of repeat examinations. The claimed invention (e.g.,

⁴ See Exhibit 7, 8 and 9

VoLumen®) has been used successfully in the pediatric population to evaluate the small bowel for disease using MR, as well as CT Enterography⁵.

25. To the best of my knowledge, VoLumen® is the only commercially available oral contrast agent that can be used in conjunction with Capsule Endoscopy, thus satisfying another long felt need in the art.⁶

26. I understand that the Examiner has rejected the claimed invention, in whole or in part, based on Lefere *et al.* (US Publ. No. 2005/0175542). I am a named co-inventor of this published patent application. E-Z-EM Inc. is the assignee of record of both the present application and the Lefere publication. I was employed by E-Z-EM at the time of invention for each of these applications. Philippe Lefere, the other named co-inventor, was a paid consultant for E-Z-EM, with whom I worked in developing the claimed method for tagging colonic residue in an individual, as claimed in the Lefere publication.

27. In rejecting the claimed invention, I understand that the Examiner relied on certain portions of ¶¶s 27, 30, 31, 40 and 65 of the Lefere publication. I am the sole inventor of and conceived the subject matter set forth in the relevant portions of those paragraphs prior to April 6, 2002, which is the filing date of the provisional application of the Lefere patent application. Specifically, the relevant portions of the above-mentioned paragraphs which I conceived include a contrast agent comprising barium-sulfate in doses from 0.1% w/v and higher; and combining such a formulation with a sugar-based compound, viscosity agents,

⁵ See Exhibit 10, 11, 12 and 13

⁶ See Exhibit 14, 15 and 16

and/or gums. The sugar-based compound preferably is sorbitol, in an amount from 0.1% to about 3% by volume. The formulations being orally administered, and images of an individuals' gastrointestinal tract (e.g., colon) may be screened for abnormalities (e.g. cancer).

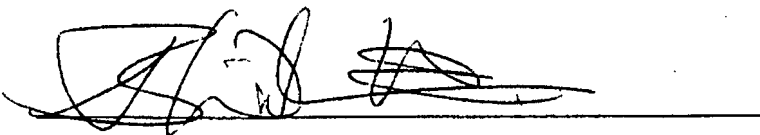
28. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Archie Williams

Date: _____

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28. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Archie Williams

Date: Dec 6, 2007